## REMARKS

### I. The Invention

The present invention describes a recombinant vector useful for inducing a tumor-specific immune response against B-cell lymphoma, by way of a fusion protein of a cytokine and a tumor-specific idiotype. Rather than directly encoding the fusion protein, which would require individual cloning of the idiotype of every patient's lymphoma cells, the expression vector of this invention includes a sequence of at least 1.5 kb that is homologous to an at least 1.5 kb segment of the $\mu$ intron or the $k$ intron, such that, following transfection of a B lymphoma cell and subsequent homologous recombination, the DNA sequences coding a cytokine and a immunoglobulin constant region (or a part thereof) also present in the vector are incorporated into the malignant B cell's genomic sequence. A cytokine fusion protein is then produced by the B cell to include the specific idiotype encoded by the endogenous sequence of the malignant B cell. After rendered incapable of proliferation, such a malignant B cell expressing a tumor immunoglobulin-cytokine fusion protein can be reintroduced into a patient to elicit a specific anti-B cell lymphoma immunity due to enhanced recruitment of antigen-presenting cells by the cytokine and more effective presentation of the tumor-specific immunoglobulin idiotype. This invention eliminates the need to clone each patient's idiotypic domain and is thus quick, convenient, and less expensive.

### II. Status of the Claims

Claims 1-5, 7-9, 11-17, and 29 are pending and stand rejected.

### III. Claim Rejections

A. 35 U.S.C. §112, First Paragraph: Written Description

Claims 1-5, 7-9, and 11-17 are rejected under 35 U.S.C. §112, first paragraph, for alleged inadequate written description. Applicant respectfully traverses the rejection for reasons already made of record in Applicant's earlier responses.

To reiterate Applicant's position, the pending claims are drawn to a vector for expressing immunoglobulin-cytokine fusion proteins in malignant B cells. The vector comprises the following components operably linked to each other: (a) a region of at least 1.5 kb that is homologous to an at least 1.5 kb segment of the $\mu$ intron or the $k$ intron; (b) at least one DNA sequence encoding a constant region of an immunoglobulin or a part of the constant region; (c) a DNA sequence encoding a cytokine; and (d) a marker gene that is selectable in eukaryotic B cells and contains a functional enhancer region. At the effective filing date of this application, all of these common components of the claimed vector--$\mu$ or $k$ intron sequence, immunoglobulin constant region sequence, cytokine sequences, selectable marker sequences, and enhancer sequences, were well known and available to a person of ordinary skill in the art. An artisan upon reading the present disclosure would then reasonably conclude that the present inventor had in his possession these components and therefore the claimed vector. As such, the present disclosure meets the written description requirement, which requires a patent specification to describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention at the time of filing.

On page 3 of the Office Action mailed April 3, 2008, the Examiner again cites *University of Rochester v. G.D. Searles & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004) and *Ex parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007), and argues that the written description requirement is not met merely by demonstrating one's ability to possess the claimed invention. The Examiner stresses the distinction between the ability to obtain the invention and the inventor's being in possession of the invention. Applicant understands this distinction and, based on this understanding, Applicant contends that the instant disclosure demonstrates both a skilled artisan's ability to obtain the invention and inventor's being in possession of the invention. Unlike in *Rochester* or *Kubin*, the broad genera of $\mu$ or $k$ intron sequences, immunoglobulin constant region sequences, cytokine sequences, selectable marker sequences, or enhancer sequences were well known in the art. The Examiner's analysis of "representative number of species" or "common structural features" and conclusion thus have no relevance in the present case.

In short, the written description rejection stands for the proposition that an artisan of ordinary skill would not be convinced of Applicant's possession of the claimed vector, even though the components of the vectors, $\mu$ or *k* intron sequences, immunoglobulin constant region sequences, cytokine sequences, selectable marker sequences, and enhancer sequences, were all known in the art at that time. This is not a tenable position. Furthermore, the large number of possible selections within each genus of ***known*** components is evidence of a broad scope of enablement and possession of the invention, not remotely akin to the "hunting" for the unknown referred to by the Supreme Court in *Brenner*. Contrary to the Examiner's position, one's ability to choose from a broad range of ***known*** components to practice a claimed invention in fact supports the conclusion of inventor's having possession of the invention.

For these reasons as well as those already made of record in Applicant's previous responses, it is respectfully submitted that the instant application has fully met the written description requirement under 35 U.S.C. §112, first paragraph. It is therefore respectfully requested that the Examiner withdraw the written description rejection.

B. 35 U.S.C. §102

Claims 1-5, 7-9, 11, 13-17, and 29 are rejected for alleged anticipation under 35 U.S.C. §102(e) by Polack *et al.* (U.S. Patent No. 6,521,449) as evidenced by Mucke *et al.* (*Gene Therapy* 4:82-92, Feb. 1997). Applicant respectfully traverses the rejection.

Applicant contends that not neither Polack nor Mucke provides all limitations of the pending claims. For instance, the limitation of "a region of at least 1.5 kb which is homologous to an at least 1.5 kb segment of the $\mu$ intron or the *k* intron" can be found in neither of the two references. The Examiner argues that the limitation is provided, because Polack describes the combined use of two enhancer $\kappa$ intron elements, Ei and E3' enhancers, which provide a combined length of over 1.5 kb. The Examiner points to Figure 1(b) of Mucke as evidence to support this position. There are at least two reasons why the pending claims are not anticipated by Polack/Mucke, because this limitation is indeed missing from Polack/Mucke.

First, the limitation of "a region of at least 1.5 kb which is homologous to an at least 1.5 kb segment of the $\mu$ intron or the *k* intron" as used in the claims should be properly construed as requiring "a region of at least 1.5 kb" and "an at least 1.5 kb segment of the $\mu$ intron or the *k* intron." to be ***continuous***. The specification explains that such homologous region is necessary for inserting the coding sequences for the cytokine, immunoglobulin constant region (or portion thereof), and selective marker into the target malignant B cell genome via site-specific homologous recombination, and that the homologous sequence must have a length of at least 1.5 kb to ensure successful recombination. See, *e.g.*, the paragraph bridging pages 5-6, and the last paragraph on page 10. Thus, a person of skill in the art upon reading the specification would recognize beyond any doubt that the "region of at least 1.5 kb" and the " at least 1.5 kb segment of the $\mu$ intron or the *k* intron" are inherently continuous, as otherwise there would be no recombination, let along any site-specific recombination. Polack/Mucke placed the Ei and E3' enhancers immediately adjacent to each other in vector BC219. But even if this placement does produce a combined length of over 1.5 kb as alleged by the Examiner, it is NOT a continuous length of the $\mu$ or *k* intron as inherently required by the limitation of "a region of at least 1.5 kb which is homologous to an at least 1.5 kb segment of the $\mu$ intron or the *k* intron." Furthermore, Applicant does not agree with the Examiner's assertion that that Figure 1 (b) of Mucke shows the *k* E3' enhancer to be approximately 881 bp in length and the *k* Ei enhancer to be approximately 1486 kb (sic) in length (see last paragraph on page 7 of the Office Action mailed April 3, 2008). Figure 1(b) in fact shows the E3' enhancer to be longer than the Ei enhancer: the Ei enhancer is no more than 800 bp (EcoRI 3070 to XbaI 3817) and the E3' enhancer is about 1200 bp (XbaI 3817 to BamHI 5025). None of these two enhancers are "at least 1.5 kb" in length.

Second, at least one the two enhancers used by Polack/Mucke, the E3' enhancer, does not belong to a "segment of the $\mu$ intron or the *k* intron." The E3' enhancer, according to Mucke, is located 3' to the human Ig kappa light chain gene locus, see legend of Figure 1(b). This description indicates that the E3' enhancer is not a part of the *k* intron, as introns are by definition untranslated sequences within a gene, not sequences located at a position 3' to the

gene. Thus, the construct shown in Figure 1(b) does not provide the limitation of "a region of at least 1.5 kb which is homologous to an at least 1.5 kb segment of the $\mu$ intron or the *k* intron."

At least for these reasons, Polack/Mucke cannot anticipate the pending claims. Withdrawal of the rejection under 35 U.S.C. §102(e) is therefore respectfully requested.

C. 35 U.S.C. §103

Claims 1-5, 7-9, 11-13, and 15-17 are rejected under 35 U.S.C. §103 for alleged obviousness over Polack in view of Levy and Gillies. Claims 1-5, 7-9, and 11-17 are further rejected under 35 U.S.C. §103 for alleged obviousness over Polack or Mucke in view of Mocikat (*Immunology* **84**:159-163, 1995). Applicant respectfully traverses the rejections.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143. As discussed above, neither of the primary references by Polack *et al.* and Mucke *et al.* provide all limitations of the pending claims. On the other hand, the secondary references, Levy, Gillies, and Mocikat, are cited to provide teaching of a vector encoding an idiotype/GM-CSF fusion protein, a vector encoding a recombinant antibody-cytokine fusion protein, and a vector for homologous recombination at the Ig locus, respectively (see page 16 of the Office Action mailed March 5, 2007, and pages 9-10 of the Office Action mailed October 18, 2007). None of the Levy and Gillies references provide at least one missing element, namely the region of at least 1.5 kb which is homologous to an at least 1.5 kb segment of the $\mu$ intron or the *k* intron as recited in (a) of claim 1. Without providing all claim limitations, the cited references cannot support a *prima facie* case of obviousness.

The Examiner argues that, since Mocikat *et al.* included of a 2.3 kb fragment of the mouse $\mu$ intron sequence in their recombination vector, the missing claim limitation is supplemented (page 11 of the Office Action mailed April 3, 2008). Applicant understands the Examiner's argument that a 2.3 kb fragment meets the requirement of "at least 1.5 kb."

Nevertheless, an artisan upon reading Polack, Mucke, and Mocikat together would still have no reason or motivation to replace the enhancers used by Polack with the 2.3 kb $\mu$ intron sequence used by Mocikat to modify Polack's expression vector. This is because Polack used the enhancers to facilitate or augment the expression of a gene of interest, and replacing the enhancers with the 2.3 kb intron sequence would completely defeat this purpose. As such, there is at least one obvious reason to NOT combine Polack, Mucke, and Mocikat. No *prima facie* obviousness is or can be established.

Accordingly, Applicant respectfully request withdrawal of the rejections under 35 U.S.C. §103(a).

## CONCLUSION

In view of the foregoing, Applicant believes that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Chuan Gao
Reg. No. 54,111

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
CG:cg
61510216 v1